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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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|---|---|
| RAWLINGS, STEPHEN L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | 10 |

DATE MAILED: 07/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/768,840 | HILLMAN ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Peri d for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2003 and 05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *1,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14 and 21-26* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

## DETAILED ACTION

1. The supplemental election with traverse filed May 5, 2003 in Paper No. 9 is acknowledged and has been entered. Applicants have elected the species of the generic invention of Group II, claims 2-12 and 21-26, wherein said fragment of a polypeptide having the amino acid sequence set forth in SEQ ID NO: 1 is a fragment comprising residues D254-V266 of SEQ ID NO: 1.

2. The election filed March 5, 2003 in Paper No. 5 was acknowledged in the Office action mailed April 11, 2003 (Paper No. 8); however, the Examiner erroneously recorded in that Office action that Applicants' election is to be treated as an election without traverse, since Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement. As Applicants' have remarked in the supplemental election filed May 5, 2003, Applicants' election filed March 5, 2003 in Paper No. 5 was made with traverse; and it is noted that Applicants have reiterated those grounds of traversal in the election filed May 5, 2003. Therefore, Applicants' grounds of traversal in Paper Nos. 5 and 9 are acknowledged and have been addressed below.

3. Claims 1-14 and 21-26 are pending in the application. Claims 1, 13, and 14 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

For clarity of record, it is noted that in section 3 of the Office action mailed April 11, 2003 (Paper No. 8) the Examiner inadvertently omitted claim 1 from the list of claims that have been withdrawn from further consideration; claim 1 has been withdrawn pursuant to 37 CFR § 1.142(b), as being drawn to a non-elected invention. Accordingly, contrary to the statement in section 4 of the Office action mailed April 11, 2003, claim 1 was not subject to further restriction, as evidenced by the absence of claim 1 in section 5, which sets forth the further restriction and election requirement.

4. Claims 2-12 and 21-26, insofar as the claims are drawn to the elected species of invention, are currently under prosecution.

***Election/Restrictions***

5. Applicant's election with traverse of the invention of Group II in Paper No. 5 is acknowledged. Applicants have traversed the restriction arguing that restriction is improper if the restricted inventions can be searched without serious burden. More specifically, Applicants have argued that the claims drawn to the product of the claim 1, namely a polypeptide, and the claims drawn to the elected invention, namely an antibody that binds the polypeptide should be examined together because the search required to examine both inventions is not undue. Additionally, Applicants have argued that claims drawn to a product should be examined together with claims drawn to a method for using the product.

Applicant's election with traverse of the species of the invention of Group II in Paper No. 9 is also acknowledged. Applicants have traversed the restriction arguing that restriction is improper if the restricted inventions can be searched without serious burden. Applicants have contended that each of the claimed species of invention can be searched without undue burden because the separate required searches would produce overlapping results.

Applicants' grounds of traversal have been carefully considered but not found persuasive. The inventions are distinct for the reasons set forth in the Office action mailed February 24, 2002 (Paper No. 4); and because the search that would be required to examine any one invention is not co-extensive with the search that would be required to examine any other, the restriction is proper. Regarding the requirement to elect a species of invention, the search that would be required to examine any one species of invention is not co-extensive with the search that would be required to examine any other; therefore, the requirement is proper.

Applicants have remarked that the requirement to elect a species of invention is improper because the Office action failed to provide reasons that the species of

invention are patentably distinct. The requirement to elect a species of invention was set forth because searching more than one species of invention would require a burdensome search; moreover, the resources and facilities of the Office are currently insufficient to enable a search of more than one species of invention without undue burden. If no prior art were to have been discovered in searching the elected species of the claimed invention, it would have been proper to conduct additional searches until relevant prior art is discovered that anticipates or renders obvious a claimed species of invention, or until the generic claim is determined to be novel and unobvious.

Furthermore, as noted in the Office action mailed April 11, 2003 (Paper No. 8), should Applicants traverse on the ground that the species are not patentably distinct, Applicants should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. Applicants have remarked in the election filed May 5, 2003 (Paper No. 9), "each of the restricted species are **examples** of antibodies which specifically bind calcium-binding fragments of SEQ ID NO:1" (page 7, paragraph 2; emboldened and underlined in the original). This statement, however, has not been construed as a clear admission on the record that the species of invention are obvious variants of one another.

Regarding Applicants' argument that claims drawn to a product and a process of using said product should be examined together, it is proper to restrict such claims into distinct groups of inventions, provided the inventions can be shown to be distinct. The inventions can be shown to be distinct, each from the other, if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). As noted in the Office action mailed February 24, 2003, the inventions are distinct because the product as claimed, namely an antibody can be used in a materially different process of using that product, such as the different methods of claims 13 and 14, as

originally filed. However, process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Amendments, which are submitted after final rejection, are governed by 37 CFR § 1.116. Process claims that do not depend from or otherwise include the limitations of the patentable product will be withdrawn from consideration, via an election by original presentation, as per MPEP § 821.03. Amendments, which are submitted after allowance, are governed by 37 CFR § 1.312. Process claims, which depend from or otherwise include all the limitations of an allowed product claim and which meet the requirements of 35 U.S.C. §§ 101, 102, 103, and 112, may be entered.

The restrictions and election requirements set forth in the Office actions mailed February 24, 2003 (Paper No. 4) and April 11, 2003 (Paper No. 8) are still deemed proper and are therefore made FINAL.

***Priority***

6. Applicants' claim to the benefit of the earlier filing dates of US Application No. 09/206,499, upon which has now issued as US Patent No. 6,194,385 B1, and US Application No. 08/828,242, upon which has now issued US Patent No. 5,871,970 A, is acknowledged; however, because the subject matter of the claimed invention is not disclosed therein, so as to have meet the requirements set forth under 35 USC §112, first paragraph, claims 4, 6-9, and 21-23 have not been given the claimed benefit of the filing dates of either application. As such, the earliest date to which this claims 4, 6-9, and 21-23 are given benefit is January 23, 2001, or the filing date of the instant application.

The particular reasons are as follows:

As US Patent No. 6,194,385 B1 states that US Application No. 09/206,499 is a division of US Application No. 08/828,242, the disclosure of the latter is presumed the same as the disclosure of the former.

Claim 4 has not been given the claimed benefit, because claim 4 recites, "an acceptable excipient", since the originally filed disclosure of US Application No.

09/206,499 does not include an adequate description of the broad genus of acceptable excipients. Rather US Application No. 09/206,499 merely discloses, "pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients" (column 20); and in this particular context, also discloses examples of "suitable excipients" (column 20).

Claims 6-9 have not been given the claimed benefit, because the claims recite method steps, which do not appear to be particularly described in the originally filed disclosure of US Application No. 09/206,499. Although claim 5 of US Patent No. 6,194,385 B1 recites similar, if not identical method steps as those that are recited in claim 8 of this application, it appears that the originally filed US Application No. 09/206,499 does not.

Claim 21 has not been given the claimed benefit, because the claim recites: "A composition of claim 4, further comprising a label." US Application No. 09/206,499 merely discloses: "The antibodies may be used with or without modification, and may be labeled by joining them, either covalently or non-covalently, with a reporter molecule" (column 22). Thus, the application, as originally filed, does not appear to describe a composition comprising an antibody and further comprising a label, but only such a composition where the antibody is joined to the label.

Claims 22 and 23 have not been given the claimed benefit, because the claims recite, "a suitable carrier". As originally filed, US Application No. 09/206,499 describes "a suitable pharmaceutical carrier", but does not disclose "a suitable carrier", *per se*; and the disclosure of suitable pharmaceutical carriers is not deemed sufficient to describe the broader genus of suitable carriers.

***Lack of Compliance with Sequence Rules***

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence

And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

As indicated on the attached Notice to Comply, the specification discloses amino acid sequences, which are each of sufficient length, i.e., an unbranched chain of at least four specifically identified amino acids, to fall under the requirements set forth in 37 CFR §§ 1.821-1.825, at page 1 in lines 27 and 28, respectively. Applicants are required to amend the specification to identify each disclosure of such sequences with a sequence identification number that corresponds to the same sequence set forth in the Sequence Listing; if necessary, Applicants are required to submit substitute copies of the Sequence Listing, including the sequences, and a statement that both copies are the same and include no new matter.

Applicants are given the same period of time within which to reply to this Office to place this application in compliance with the Sequence Rules set forth under 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Applicants are requested to return a copy of the attached Notice to Comply with the response.

***Specification***

8. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Perkin Elmer™ (page 4), Incyte™ (page 10), Amersham™ (page 12), GIBCO BRL (page 12), Hamilton™ (page 12), Clontech™ (page 13), Stratagene™ (page 16), Promega™ (page 16), Immunex™ (page 21), Invitrogen™ (page 21), Trizol™ (page 35), GENBANK (page 36), Kodak™

(Page 40), Nytran™ (page 40), Schleicher & Schuell™ (page 40), Phosphorimager™ (page 40), Molecular Dynamics™ (page 40), and Sigma™ (page 42).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

9. The specification is objected to because of the following informalities:

(a) At page 2, line 8, "calcium-bind", rather than "calcium-binding has been erringly used; and

(b) "Phosphorimager™" is misspelled at page 40, line 26.

***Claim Objections***

10. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 5 recites, "wherein the antibody is an antagonist of a polypeptide comprising the amino acid sequence of SEQ ID NO:1", but it appears that this property of the antibody of claim 2 would be an inherent property. As such, claim 5 does not appear to further limit the subject matter of claim 1, from which claim 14 depends.

***Claim Rejections - 35 USC § 101***

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 2-12 and 21-26 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The instant application provides a description of a polynucleotide sequence encoding a protein. The protein, which has the predicted amino acid sequence set forth in SEQ ID NO: 1, is what is termed in the art, an "orphan protein". This is a protein that is encoded by a complementary DNA (cDNA) molecule, which has been isolated by virtue of its having a polynucleotide sequence having similarity to other known cDNA molecules. The observed similarity between the polynucleotide sequences, or the amino acid sequences encoded thereby often leads to speculation that the protein will be found to have a particular function. In this instance, the polynucleotide sequence encoding SEQ ID NO: 1 is similar to the polynucleotide sequence encoding reticulocalbin. Indeed, it is not unlikely that after further characterization the protein of SEQ ID NO: 1, to which the claimed antibodies must bind, will be found to have a specific utility. However, until the further characterization of the protein encoded by the newly discovered polynucleotide sequence has been completed establishing the protein's putative function, the polynucleotide sequence is only a novelty, and the claimed antibody is therefore not a finished invention having an established utility.

The instant situation is directly analogous to that which was addressed in *Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 (US Sup Ct, 1966). A novel compound, which was found to be structurally analogous to other compounds known to possess anti-cancer activity, was alleged to be useful by virtue of its structural similarity to these other useful compounds but otherwise, in the absence of factual evidence. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial

> utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. Id., at 695.

Further, the Court opined,

> [W]e are [not] blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Id., at 696.

Accordingly, as the instant claims are drawn to antibodies that bind polypeptides of, as yet, an undetermined function or biological significance, until some actual and specific significance can be attributed to the polypeptide of SEQ ID NO: 1, or *HCBP,* as it is named in the disclosure, the inventive process has not been refined or developed to a point where a specific benefit can be derived by the public from the granting of a patent upon the Applicants' application. Moreover, in the absence of any established functional or biological significance, there is no immediately obvious "patentable" use for the claimed invention. To employ the claimed antibody in the diagnosis, treatment, and prevention of disorders associated with cell proliferation, as is the asserted utility of the claimed invention, would clearly require further research, which should be regarded as constituting part of the inventive process. Because the specification does not disclose a currently available, "real world" use for the claimed antibody, the requirements set forth under 35 U.S.C. § 101 have not been met.

The existing information disclosed by Applicants' application would merely provide the artisan with an invitation to perform such investigations, which might ultimately lead to a derivation of a specific benefit, or which might not; and in either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed polynucleotide in the manner asserted to provide an immediate benefit. Although the disclosure of the claimed polynucleotide might tomorrow command the grateful attention of the public, the Court has decided:

> [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

*Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 at 696 (US SupCt, 1966).

The generic usefulness of an antibody is not disputed, as any antibody can be used, for example, as the specification asserts, to purify the polypeptides to which the antibody binds; nor does the Examiner dispute the generic usefulness of any such antibody in applications designed to monitor the expression of, or detect the polypeptide to which the antibody binds, e.g., Western blot analysis, antibody array analysis, etc. However, because an antibody is generically useful as a such a reagent, the assertion that the claimed antibody can be used as such lacks specificity, because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application is not specific to the substance and nature of the claimed antibody. See *Brenner, Comr Pats v. Manson*, 148 USPQ 689 (US SupCt, 1966).

Applicants have asserted that the polypeptide to which the claimed antibody must bind is a calcium-binding protein, as the polypeptide comprises six calcium-binding EF-hand amino acid sequence motifs. The generic usefulness of a calcium-binding moiety is not disputed; EGTA, for example, is a well-known calcium-binding agent, which has proven very useful. However, absence a particular understanding of the biologic function of the polypeptide of SEQ ID NO: 1, any assertion that the claimed invention is useful because the claimed antibody binds the polypeptide of SEQ ID NO: 1, and the polypeptide of SEQ ID NO: 1 might bind calcium, is deemed insufficient to meet the utility requirements set forth under 35 USC § 101. The public would not benefit from the disclosure of the invention in a specific and substantial manner. Any calcium-binding agent can be used to chelate calcium; and anyway, EGTA, for example, could more aptly be used as a chelating, or calcium-binding agent. Otherwise, the polypeptide of SEQ ID NO: 1 could not be immediately used in any specific and practical manner to the benefit of the public.

Applicants have asserted that the claimed invention can be used as an antagonist to inhibit the function of the polypeptide to which the antibody must bind, but only given benefit of the existing disclosure of the invention, the claimed invention cannot be regarded as practically useful in the "real-world" setting of the clinic, for example, where such an antibody might be used to treat a disorder associated with

abnormal cellular proliferation. Firstly, it is noted that Applicants have not particularly described any one disorder that might be treated, prevented, or diagnosed using such an antibody; secondly, Applicants have not shown that any disorder associated with abnormal proliferation can be treated, prevented, or diagnosed using such an antibody, and moreover, Applicants have not shown that the expression or activity of the polypeptide to which the claimed antibody must bind is associated with any particular disorder, or is causative of, or otherwise indicative of abnormal cellular proliferation.

The assertion that the claimed antibody can be used in an abstract capacity to treat, prevent, or diagnose some unspecified disorder associated with abnormal cellular proliferation lacks the necessary specificity and substantiality of an asserted utility in the chemical arts that might otherwise fulfill the requirements of 35 USC § 101, because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application could not be derived immediately and directly therefrom or without need to first complete the inventive process by performing additional experimentation to characterize the functional significance of the polypeptide of SEQ ID NO: 1, or the polynucleotide sequence encoding SEQ ID NO: 1 in the pathology or etiology of a disease, or in the pharmacology of a particular drug. To fulfill the requirements of 35 USC § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

All of the asserted utilities of the claimed invention that are disclosed in the specification are founded upon a presumption that the protein to which the antibody must bind will have activity similar to reticulocalbin, or will be associated with the etiology of a disorder of cellular proliferation, such as cancer or an hyperproliferative immune disorder. The inventor's presumption is entirely based upon database searches and sequence comparisons alone. However, the skilled artisan cannot predict whether a protein will have a particular activity simply because the protein is homologous to a protein known to have such an activity. Furthermore, the skilled artisan cannot predict whether the polypeptide of SEQ ID NO: 1 will be found

associated with etiology of cancer or an immune dysfunction, or some other disorder associated with abnormal cellular proliferation. The reasons are set forth below:

Regarding the possibility that the claimed invention might be useful, because the claimed antibody can be used to purify, or detect a polypeptide to which it binds, there are dissimilarities between the amino acid sequence set forth in SEQ ID NO: 1 and the amino acid sequence of other proteins, including reticulocalbin. The skilled artisan cannot reliably or accurately predict the effects of amino acid sequence dissimilarities. Bowie et al. (*Science* 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie et al. teaches that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) teaches the sensitivity of proteins to alterations of even a single amino acid in a sequence. This reference teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al. (*Molecular and Cellular Biology* 1988; **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. The disclosures of Burgess et al. and Lazar et al. teach that even a single amino acid substitution can often dramatically affect the biological activity and the structure-function characteristics of a protein. Thus, the function of a polypeptide cannot be predicted

upon the basis of an observed sequence similarity to another protein; nor should the function of the polypeptide be reasonably expected to be the same as that of the other.

Additionally, regarding the possibility that the claimed invention might be useful, since the claimed antibody binds a polypeptide that is similar to reticulocalbin, Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that an antibody that binds a variant of reticulocalbin having at least 80% identity to the amino acid sequence set forth in SEQ ID NO: 1 is capable of being used in any specific and substantially beneficial manner, such as treating, preventing, or diagnosing a disorder associated with abnormal cellular proliferation.

Regarding the possibility that the claimed invention might be diagnostically useful, Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease. Thus, even if data were presented showing that the polypeptide of SEQ ID NO: 1 is abnormally expressed in a cellular disorder, such data would not guarantee that that the claimed invention could be used in a specific manner to diagnose, for example, a tumor. Even if an altered level of expression of polypeptide of SEQ ID NO: 1 using the claimed invention were found to clinically significant, there is insufficient direction and guidance in the disclosure to enable the skilled artisan to use the claimed invention in a manner that could immediately benefit the public. Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s), for example, teaches many considerations that must

be made in bringing a candidate tumor marker to successful clinical application; given only the benefit of Applicants' present disclosure, the skilled artisan could not use the claimed invention without having to perform additional experimentation of such complexity and measure that the public would not have derived any specific and substantial benefit from a grant of a patent monopoly of the existing information disclosed by Applicants.

Finally, regarding the possibility that the claimed invention might be therapeutically useful, the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development* 2000; **10**: 120-127) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger et al. Bergers et al. teaches, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al., discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are

somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). The disclosure of Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering to a subject a pharmaceutical composition comprising an invention that is purported to have a desired pharmacological effect. Always the efficacy of any unproven drug regimen must be determined empirically. Therefore, in such an unpredictable art as this, because the disclosure is devoid of data generated by such empirical determinations, the skilled artisan would have to perform complex and lengthy courses of experimentation before the claimed invention might be used with any reasonable expectation of success to benefit the public.

***Claim Rejections - 35 USC § 112***

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 2-12 and 21-26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claimed invention is not supported by a specific and substantial asserted utility, or a well-established utility, as the asserted utilities are either not specific to the substance and nature of the claimed antibody or could not be practiced in a manner that might immediately benefit the public. The amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims. Because the art is so highly unpredictable, in the absence of an amount of guidance, direction, and exemplification that is reasonably commensurate in

scope with the claims, the skilled artisan would not accept the assertion that the claimed invention can be used to treat, prevent, or diagnose a disorder associated with abnormal cellular proliferation. Consequently, if a patent were to issue upon this application, given only the disclosure therein, one skilled in the art would not know then how to use the claimed invention in a manner that might immediately benefit the public. As such, a patent granted upon this application could only be viewed as a mere invitation to the skilled artisan to elaborate a use for the claimed invention, or to finish the inventive process. The need to elaborate such a use, or to finish the inventive process would constitute a requirement that the practitioner perform an undue amount of experimentation before the claimed invention could be made and used in a manner that might ultimately benefit the public, or with a reasonable expectation of success.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

15. Claims 2-12, 21-23, and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-12, 21-23, and 26 are specifically drawn to a genus of isolated antibodies that bind the members of a genus of *naturally occurring* polypeptides that have an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 1. The specification includes a description of a single member of the genus of naturally occurring polypeptides, namely the polypeptide having the amino acid sequence of SEQ ID NO: 1. However, the skilled artisan could not envision, or even predict the structure of any other naturally occurring variants of the polypeptide

of SEQ ID NO: 1, which have the ability to bind calcium, even given only the benefit of the disclosure, as the structure of naturally occurring polypeptides can only be determined empirically. In the absence of a detailed description of at least a substantial number of members of the genus of naturally occurring variant polypeptides having amino acid sequences that are at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 1, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Therefore, the disclosure is insufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph.

The specification discloses a means by which other members of the genus of naturally occurring calcium-binding polypeptides having amino acid sequences that are at least 80% identical to the amino acid sequence set forth in SEQ ID NO: 1 might be isolated and characterized. However, this disclosure does not constitute factual evidence that Applicants were in possession of the claimed invention at the time the application was filed; nor does the disclosure meet the written description requirement set forth under 35 USC § 112, first paragraph. MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential

method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

16. Claims 4, 6-9, and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that this application is a division of US Application No. 09/206,499, which was filed December 7, 1998 and has now issued as US Patent No. 6,194,385 B1; additionally, the presently attached declaration states that the instant specification is the same as the originally filed specification of US Application No. 08/828,242, which was filed March 31, 1997 and has now issued as US Patent No. 5,871,970 A. Accordingly, the disclosure of this application must be the same as the disclosures of US Application Nos. 08/828,242 and 09/206,499; and therefore any disclosures in this application that do not have proper and sufficient antecedent basis in the prior applications are regarded as new matter.

As US Patent No. 6,194,385 B1 states that US Application No. 09/206,499 is a division of US Application No. 08/828,242, the disclosure of the latter is presumed the same as the disclosure of the former.

Claim 4 recites, "an acceptable excipient". The originally filed disclosure of US Application No. 09/206,499 does not include an adequate description of the broad genus of acceptable excipients to provide proper and sufficient antecedence. US Application No. 09/206,499 merely discloses, "pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients" (column 20); and in this particular context, also discloses examples of "suitable excipients" (column 20). Accordingly, the recitation of "an acceptable excipient" in claim 4 appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC §112, first paragraph.

Claims 6-9 recite method steps, which do not appear to be particularly described

in the originally filed disclosure of US Application No. 09/206,499. Although claim 5 of US Patent No. 6,194,385 B1 recites similar, if not identical method steps, the originally filed application does not. Accordingly, the recitation in claim 4 of the method steps not explicitly or intrinsically supported by the disclosure of US Application No. 09/206,499 appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC §112, first paragraph.

Claim 21 recites: "A composition of claim 4, further comprising a label." US Application No. 09/206,499 merely discloses: "The antibodies may be used with or without modification, and may be labeled by joining them, either covalently or non-covalently, with a reporter molecule" (column 22). Thus, the application, as originally filed, does not appear to describe a composition comprising an antibody and further comprising a label, but only such a composition where the antibody is joined to the label. Accordingly, the recitation of the limitation in claim 21 appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC §112, first paragraph.

Claims 22 and 23 recite, "a suitable carrier". As originally filed, US Application No. 09/206,499 describes "a suitable pharmaceutical carrier", but does not disclose "a suitable carrier", *per se*; and the disclosure of suitable pharmaceutical carriers is not deemed sufficient to describe the broader genus of suitable carriers. Accordingly, the recitation in claims 22 and 23 of "a suitable carrier" appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC §112, first paragraph.

These grounds of rejection may be obviated if Applicants were to amend the specification to indicate that this application is a continuation-in-part of US Application No. 09/206,499 and submit a new declaration, which is appropriate to this situation. In this regard, it is noted that the disclosure should then be amended to recite proper and sufficient antecedence for any of the originally filed claim language, which is not presently supported by the instant disclosure.

Otherwise, these grounds of rejection could be obviated if Applicants were to amend the claims to recite language that is properly and sufficiently supported by the

instant disclosure and necessarily the disclosure of US Application No. 09/206,499, as both disclosures are allegedly the same. Alternatively, these grounds of rejection might be obviated if Applicants were to point to specific disclosures in the originally filed specification of US Application No. 09/206,499, which are believed to provide proper and sufficient antecedent basis for the language of the presently rejected claims.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 4, 22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the term "acceptable excipient"; and claims 22 and 23 recite the term "suitable carrier". The recitation of these terms renders the claims indefinite. The metes and bounds of the subject matter of the claims are indefinitely delineated, because "acceptable" and "suitable" are subjective terms. As to whether or not a particular excipient, or carrier is regarded by Applicants as "acceptable", or "suitable" cannot be determined by the practitioner in the absence of an explicit definition of the genus of "acceptable" excipients and an explicit definition of the genus of "suitable" carriers. Moreover, the skilled artisan might find one excipient or carrier more or less acceptable than another, depending upon how the composition is to be used, but the requisite degree to which the excipient or carrier must be acceptable or suitable is not clearly delineated; and, as the claims do not explicitly state how the composition is to be used, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that Applicants regard as the invention.

### *Claim Rejections - 35 USC § 102*

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claims 4, 7, 9, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/44114 A1 (08 October 1998).

WO 98/44114 A1 discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO: 1, and an acceptable excipient or a suitable carrier.

21. Claims 4, 7, 9, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,976,801 A (02 November 1999).

US Patent Nos. 5,976,801 A discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO: 1, and an acceptable excipient or a suitable carrier.

22. Claims 4, 7, 9, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,235,477 B1.

The applied reference has a common assignee with the instant application; additionally, the applied reference has a common inventor with the instant application, but a different inventive entity. Based upon the earlier effective U.S. filing date of the reference, the reference constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR § 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR § 1.131.

US Patent Nos. 6,235,477 B1 discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO: 1, and an acceptable excipient or a suitable carrier.

***Claim Rejections - 35 USC § 103***

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 4, 6-9, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/44114 A1 (08 October 1998) in view of Kohler et al. (*Nature* 1975; **256**: 495-497).

WO 98/44114 A1 discloses that which is set forth in the rejection of claims 4, 7, 9, 22, and 23 under 35 USC § 102(b) above. In addition, WO 98/44114 A1 discloses the preparation of antibodies by immunizing animals by injecting the animals with the polypeptide of SEQ ID NO: 1 or an immunogenic fragment thereof. WO 98/44114 A1 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the technique disclosed by Kohler et al. (1975). Furthermore, WO 98/44114 A1 discloses that antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 can be used to detect and measure the expression of the polypeptide by techniques such as radioimmunoassay.

However, WO 98/44114 A1 does not explicitly disclose that the preparation of a polyclonal antibody comprises the step of isolating antibodies from the animal following immunization, or the step of screening the isolated antibodies with the polypeptide to identify a polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1. In addition, WO 98/44114 A1 does not explicitly disclose a method for preparing a monoclonal antibody comprising the particular steps recited in the body of claim 8.

Furthermore, WO 98/44114 A1 does not explicitly disclose a composition comprising an antibody and a label.

Kohler et al. discloses a method for preparing a monoclonal antibody comprising the following steps:

(a) Immunizing an animal with a polypeptide under conditions to elicit an antibody response;

(b) Isolating antibody producing cells from the animal;

(c) Fusing the antibody-producing cells with immortalized cells in culture to form monoclonal antibody-producing hybridoma cells; and

(d) Isolating from the culture, monoclonal antibody that binds specifically to the polypeptide that was used to immunize the animal.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a monoclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the steps recited in claim 8, because WO 98/44114 A1 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the method disclosed by Kohler et al. (1975), which comprises the steps recited in claim 8. The state of the art, at the time the invention was made, was such that given the teachings of WO 98/44114 A1, it would have been *prima facie* obvious to one of ordinary skill in the art to have prepared an polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the particular steps recited in claim 6. Furthermore, as WO 98/44114 A1 teaches that the antibody can be used in a radioimmunoassay, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a composition comprising an antibody and further comprising a label by radiolabeling the antibody.

One of ordinary skill in the art at the time the invention was made would have been motivated to prepare monoclonal or polyclonal antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 using methods comprising the particular steps recited in claims 6 and 8, because Kohler et al., for example, teaches that such methods can

be used to successfully prepare a monoclonal antibody that binds specifically to a polypeptide and WO 98/44114 A1 teaches that such antibodies are useful reagents, provided the antibodies have the necessary specificity. One of ordinary skill in the art at the time the invention was made would have been motivated to prepare a composition comprising a radiolabled antibody, for example, that binds specifically to the polypeptide of SEQ ID NO: 1 for use in a radioimmunoassay to detect the polypeptide in a sample.

25. Claims 4, 6-9, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,976,801 A in view of Kohler et al. (*Nature* 1975; **256**: 495-497).

US Patent No. 5,976,801 A ('801) discloses that which is set forth in the rejection of claims 4, 7, 9, 22, and 23 under 35 USC § 102(b) above. In addition, '801 discloses the preparation of antibodies by immunizing animals by injecting the animals with the polypeptide of SEQ ID NO: 1 or an immunogenic fragment thereof. '801 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the technique disclosed by Kohler et al. (1975). Furthermore, '801 discloses that antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 can be used to detect and measure the expression of the polypeptide by techniques such as radioimmunoassay.

However, '801 does not explicitly disclose that the preparation of a polyclonal antibody comprises the step of isolating antibodies from the animal following immunization, or the step of screening the isolated antibodies with the polypeptide to identify a polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1. In addition, '801 does not explicitly disclose a method for preparing a monoclonal antibody comprising the particular steps recited in the body of claim 8. Furthermore, '801 does not explicitly disclose a composition comprising an antibody and a label.

Kohler et al. discloses a method for preparing a monoclonal antibody comprising the following steps:

(a) Immunizing an animal with a polypeptide under conditions to elicit an antibody response;

(b) Isolating antibody producing cells from the animal;

(c) Fusing the antibody-producing cells with immortalized cells in culture to form monoclonal antibody-producing hybridoma cells; and

(d) Isolating from the culture, monoclonal antibody that binds specifically to the polypeptide that was used to immunize the animal.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a monoclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the steps recited in claim 8, because '801 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the method disclosed by Kohler et al. (1975), which comprises the steps recited in claim 8. The state of the art, at the time the invention was made, was such that given the teachings of '801, it would have been *prima facie* obvious to one of ordinary skill in the art to have prepared an polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the particular steps recited in claim 6. Furthermore, as '801 discloses that the antibody can be used in a radioimmunoassay, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a composition comprising an antibody and further comprising a label by radiolabeling the antibody.

One of ordinary skill in the art at the time the invention was made would have been motivated to prepare monoclonal or polyclonal antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 using methods comprising the particular steps recited in claims 6 and 8, because Kohler et al., for example, teaches that such methods can be used to successfully prepare a monoclonal antibody that binds specifically to a polypeptide and '801 discloses that such antibodies are useful reagents, provided the antibodies have the necessary specificity. One of ordinary skill in the art at the time the invention was made would have been motivated to prepare a composition comprising a radiolabled antibody, for example, that binds specifically to the polypeptide of SEQ ID NO: 1 for use in a radioimmunoassay to detect the polypeptide in a sample.

26. Claims 4, 6-9, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,235,477 B1 in view of Kohler et al. (*Nature* 1975; **256**: 495-497).

US Patent No. 6,235,477 B1 ('477) discloses that which is set forth in the rejection of claims 4, 7, 9, 22, and 23 under 35 USC § 102(e) above. In addition, '477 discloses the preparation of antibodies by immunizing animals by injecting the animals with the polypeptide of SEQ ID NO: 1 or an immunogenic fragment thereof. '477 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the technique disclosed by Kohler et al. (1975). Furthermore, '477 discloses that antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 can be used to detect and measure the expression of the polypeptide by techniques such as radioimmunoassay.

However, '477 does not explicitly disclose that the preparation of a polyclonal antibody comprises the step of isolating antibodies from the animal following immunization, or the step of screening the isolated antibodies with the polypeptide to identify a polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1. In addition, '477 does not explicitly disclose a method for preparing a monoclonal antibody comprising the particular steps recited in the body of claim 8. Furthermore, '477 does not explicitly disclose a composition comprising an antibody and a label.

Kohler et al. discloses a method for preparing a monoclonal antibody comprising the following steps:

(a) Immunizing an animal with a polypeptide under conditions to elicit an antibody response;

(b) Isolating antibody producing cells from the animal;

(c) Fusing the antibody-producing cells with immortalized cells in culture to form monoclonal antibody-producing hybridoma cells; and

(d) Isolating from the culture, monoclonal antibody that binds specifically to the polypeptide that was used to immunize the animal.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a

monoclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the steps recited in claim 8, because '477 discloses that monoclonal antibodies to the polypeptide of SEQ ID NO: 1 may be prepared using, for example, the method disclosed by Kohler et al. (1975), which comprises the steps recited in claim 8. The state of the art, at the time the invention was made, was such that given the teachings of '477, it would have been *prima facie* obvious to one of ordinary skill in the art to have prepared an polyclonal antibody that binds specifically to the polypeptide of SEQ ID NO: 1 by a method comprising the particular steps recited in claim 6. Furthermore, as '477 discloses that the antibody can be used in a radioimmunoassay, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared a composition comprising an antibody and further comprising a label by radiolabeling the antibody.

One of ordinary skill in the art at the time the invention was made would have been motivated to prepare monoclonal or polyclonal antibodies that bind specifically to the polypeptide of SEQ ID NO: 1 using methods comprising the particular steps recited in claims 6 and 8, because Kohler et al., for example, teaches that such methods can be used to successfully prepare a monoclonal antibody that binds specifically to a polypeptide and '477 discloses that such antibodies are useful reagents, provided the antibodies have the necessary specificity. One of ordinary skill in the art at the time the invention was made would have been motivated to prepare a composition comprising a radiolabled antibody, for example, that binds specifically to the polypeptide of SEQ ID NO: 1 for use in a radioimmunoassay to detect the polypeptide in a sample.

***Double Patenting***

27. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

28. Claims 2, 4, 5-9, and 22-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 5 of US Patent No. 6,194,385 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other. In practicing the method of claim 5 of US Patent No. 6,194,385 B1, the practitioner would practice the method of claim 8 of the instant application and would thereby prepare the antibody of claim 9 of the instant application. In practicing the methods of claims 4 and 5 of US Patent No. 6,194,385 B1, the practitioner would necessarily prepare an antibody that meets the limitations of claims 2, 4, 5, 7, 9, and 22-26. Furthermore, although claim 4 of US Patent No. 6,194,385 B1 is not specifically drawn to a method for preparing a polyclonal antibody, whereas claims 6 and 7 of the instant application are drawn to such a method and the antibody so prepared, it would be obvious to use the method of claim 4 of US Patent No. 6,194,385 B1 to prepare a polyclonal antibody. Additionally, although claim 4 of US Patent No. 6,194,385 B1 does not recite a step in which the isolated antibodies are screened to identify the polyclonal antibody having the required specificity, it would be obvious to do so in practicing the method of claim 4 of US Patent No. 6,194,385 B1, as the objective to practicing the latter is to prepare an antibody that binds a protein comprising the amino acid sequence set forth in SEQ ID NO: 1.

***Conclusion***

29. No claims are allowed.

30. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure. WO 99/1438 A2, WO 99/07849 A2, WO 00/53758 A2, WO 99/33979 A2 (cited by Applicants), WO 01/04311 A1, and WO 98/42738 A1 (cited by Applicants) teach antibodies that bind polypeptides similar or identical to the polypeptide of SEQ ID NO: 1.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

S Rawlings
STEPHEN RAWLINGS

slr
July 23, 2003

| Notice to Comply | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/768,840 | HILLMAN ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The specification discloses amino acid sequences, which are each of sufficient length, i.e., an unbranched chain of at least four specifically identified amino acids, to fall under the requirements set forth in 37 CFR §§ 1.821-1.825, at page 1 in lines 27 and 28, respectively. If necessary, Applicants are required to submit substitute copies of the sequence listing and the statement, as indicated below.

### Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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